

**Rituximab and brentuximab vedotin with deferred BMT for relapsed classical Hodgkin lymphoma**

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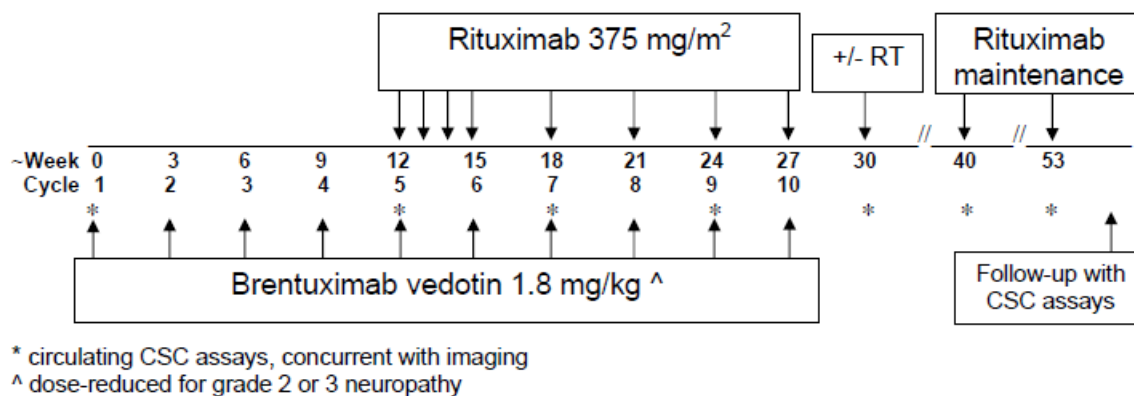
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**SCHEMA**

Note: A response to 4 cycles of brentuximab vedotin is required to continue study treatment.

**1.0 INTRODUCTION****1.1 Study overview**

Curative but less toxic regimens are needed for patients with relapsed classical HL (cHL). Salvage chemotherapy followed by high-dose therapy with autologous blood or marrow transplantation (auto BMT) is the standard approach for first chemosensitive relapse of cHL. Although auto BMT in this context is curative in approximately 40% of cases, it carries risks of major morbidity, a 5-8% mortality risk, and a nearly 100% risk of infertility. **This pilot study explores a completely novel platform for the first-line management of relapsed cHL, based on a) the concept of targeting cancer stem cells (CSCs) as well as tumor bulk, and b) avoidance of high-dose cytotoxic therapy and BMT for chemosensitive relapse.**

Although Hodgkin/Reed-Sternberg (HRS) cells in cHL usually lack B-cell markers including CD20, this disease is now widely recognized to be a B-cell malignancy. Yet, single-agent rituximab has clinical activity in cHL, even in the cases where HRS lack CD20 expression.<sup>1</sup> Our group at Johns Hopkins has found that, in patients with cHL, circulating clonotypic malignant cells with stem cell properties express CD20. We have shown that rare, clonotypic, malignant B cells circulate in the blood of most patients with active cHL, including patients with limited-stage disease.<sup>2</sup> These clonotypic B-cells have the same immunoglobulin gene rearrangements as lymph node-derived HRS cells and hence are clonally related. However, unlike HRS cells, these clonotypic cells lack CD30 while expressing memory B-cell markers including CD20. These findings potentially explain the clinical activity of rituximab in cHL, including cases lacking CD20 expression on HRS cells,<sup>1,3</sup> and raise the possibility that anti-B-cell therapies represent new approaches for this disease.

A convergence of clinical observations and laboratory-based work on tumor stem cells in B lineage malignancies thus suggests a potential role for rituximab in the management of cHL. A rare, distinct B-cell population in cHL with clonogenic capacity has been identified. This population, isolated by our group from patients as well as cell lines, is phenotypically distinct from HRS cells and expresses B-cell markers including CD20 and CD27.<sup>2</sup> The possibility that *in vivo* as in cell lines, cHL is sustained through "CSCs" that express B-cell markers including CD20 raises the possibility that rituximab, and perhaps other B-cell targeted therapies, may be effective in HL. Furthermore, our work at Johns Hopkins has shown that, in select patients with first chemosensitive relapse of cHL, prolonged remissions can be achieved with intensive therapy that does not involve auto

BMT.<sup>4</sup> These findings form the basis of the present trial for relapsed cHL, investigating targeted approaches that include anti-B-cell therapy without BMT as first management of relapsed chemosensitive cHL.

In a disease such as HL with a substantial cure rate, large studies carried out over many years are required to definitively address clinical questions. The size, duration and expense of these studies mean that it will be possible to evaluate very few questions efficiently in this fashion. Small studies such as this, to shed light on the potential clinical activity of new targeted therapies, to help clarify the biology of the tumor and to help identify useful tumor markers will be required to optimally define strategies to be evaluated in large clinical trials.

## 1.2 **CSCs as therapeutic targets**

### 1.21 **The CSC concept**

At least two distinct functional groups of cells of tumor lineage are recognized in many cancers.<sup>5,6</sup> It has been appreciated that many cancers, potentially including HL, are comprised of cells that may be functionally divided into these two groups: 1) relatively differentiated cells that form the bulk of the tumor but that lack significant renewal capacity, and 2) cells that may be quite distinct phenotypically but retain the capacity to self-renew and produce differentiated progeny.<sup>7</sup> The term “CSCs” is used to designate the latter, self-renewing cells which are biologically distinct from the bulk of the tumor cells and are responsible for initiating and sustaining the malignancy. Chronic myeloid leukemia is an example of such a tumor, where in the chronic phase mature granulocytes form the bulk of the tumor but are terminally differentiated and non-clonogenic.<sup>8</sup> Characterizing the CSC population profoundly affects the development of new targeted therapies. This is because stem cells may differ markedly in phenotype and drug sensitivity from the cells that compromise the bulk of the tumor. Although the clinical significance of CSCs remains hotly debated, therapies might be more likely to result in long-term remissions if, in addition to reducing overall disease bulk, they also inhibit the cells responsible for disease maintenance.<sup>5</sup> Few clinical trials have investigated CSC targeting. *It is hypothesized that strategies that target the more apparent, differentiated cells (to reduce tumor bulk) combined with strategies that target CSCs represent a new potential approach to improving progression-free survival (PFS).*

### 1.22 **Evaluating CSC therapies**

One of the central challenges posed by the stem cell conceptual framework is that as new targeted therapies are investigated, remission induction is not necessarily informative in terms of cure, and that in some circumstances cure might be achieved before radiographic remission is achieved. In HL it has long been recognized that fibrotic tumor masses may persist (leading to evidence of disease by conventional radiographic assessment) even in patients who have been cured; hence the importance of progression-free survival endpoints.

However, fibrosis is not the only potential confounding factor in assessing treatment response. Long lived malignant cells that are not stem cells may in theory be detected in a variety of laboratory or radiographic tests even after the CSC compartment has been ablated. For example, glucose metabolism may persist leading to signal on 18-F-FDG-PET. In HL this is even more of an issue than in other tumors because the FDG-PET signal may not even originate in tumor lineage cells but may originate in the benign, infiltrating lymphocytes that comprise the bulk of the tumor. FDG-PET would seem to be a reliable marker so long as CSCs, bulk tumor cells, and cells of the benign inflammatory infiltrate are eradicated in concert. That seems to be the case with present chemotherapies, as it has been recently appreciated that FDG-PET is remarkably predictive in HL.<sup>9</sup> However, as

more targeted therapies are explored, this parallel sensitivity may cease to exist; stem cells may be targeted more effectively by one therapy while bulk tumor cells are more effectively targeted by another. Other approaches to gauging the efficacy of such treatments are therefore needed and form a basis for this trial's correlative studies, wherein the clinical utility of CSC assays (frequency of circulating clonotypic B cells) is investigated. Specimens from this trial will be used to help begin to assess the clinical value of monitoring frequencies of circulating clonotypic B cells in the context of a potential stem cell targeting therapy. This is anticipated to provide a framework for evaluating subsequent studies of stem cell directed therapies for cHL.

### 1.3 **Targeting B cells in cHL**

#### 1.31 **The B-cell origin of cHL**

The B-cell origin of cHL has only relatively recently been widely appreciated. It was long obscured by the peculiar architecture of the involved nodes with their dense polymorphous infiltrates, the absence of surface immunoglobulin (Ig) gene expression on HRS cells, as well as the paucity of surface B-cell markers on the HRS cells. Ig gene rearrangement studies importantly suggest that RS cells in cHL represent a monoclonal expansion of a germinal center B-cell.<sup>10,11</sup> B-cell antigens therefore represent potential new therapeutic targets for this disease, including CD20 as discussed below.

#### 1.32 **CD20 as a target in cHL**

In contrast to lymphocyte-predominant HL, most of the tumor in cHL is comprised of a benign inflammatory infiltrate including B cells and activated T cells, with relatively few interspersed RS cells. Notably, although a minority of malignant cells in cHL express CD20, rituximab can produce clinical responses even when HRS cells lack CD20 expression.<sup>1</sup> In a pilot study for multiply relapsed cHL conducted by the MD Anderson, single agent rituximab (375 mg/m<sup>2</sup> weekly for 6 weeks) produced objective responses in 22% of patients, irrespective of HRS cell CD20 expression; the median response duration was nearly 8 months (range 3-15 months).<sup>1</sup> It has been proposed that rituximab might work in cHL by depleting benign supporting B cells from the tumor microenvironment.<sup>1,12</sup>

Alternatively, we propose that rituximab might target neoplastic cHL stem cells or a B-cell population clonally related to these stem cells.<sup>2</sup> Our group at Johns Hopkins recently reported that within cHL cell lines, a small population, unlike HRS cells, has a memory B cell phenotype including CD20 and surface immunoglobulin (Ig) expression, lacks CD15 and CD30 expression, and is enriched for the stem cell marker aldehyde dehydrogenase (ALDH).<sup>2</sup> Moreover, these rare B cells appear to generate and sustain the growth of HRS cells.<sup>2</sup> In cHL pts we have also recently reported the existence of a rare, distinct clonotypic B-cell population that is phenotypically compatible with the presumed stem cell fraction identified in cHL cell lines.<sup>2</sup> *These rare, clonotypic, malignant B cells circulate in the blood of most pts with newly diagnosed cHL, including most pts with limited-stage disease.*

Although the circulating CD19<sup>+</sup> cells (as well as the CD19<sup>+</sup> ALDH<sup>low</sup> cells) displayed a normal ratio of CD27 and Ig light chain restriction, the CD19<sup>+</sup> ALDH<sup>high</sup> cells were a virtually pure population of light-chain restricted, CD27<sup>+</sup> CD30<sup>-</sup> B cells that represented a median of 0.2% (range 0-2.4%) of the total circulating CD19<sup>+</sup> cells. *Furthermore, these clonotypic B cells have the same Ig gene rearrangement as lymph node-derived HRS cells and hence are clonally related.*<sup>2</sup> Clonality was confirmed by Ig CDR3 length restriction and by DNA sequencing.<sup>2</sup> Their surface Ig expression is plausible given that, in most EBV<sup>-</sup> tumors, HRS cells have functional Ig rearrangements that appear to be epigenetically silenced.<sup>13</sup>

Interestingly, morphologically distinct subpopulations were similarly described within a human cHL cell line over 20 years ago.<sup>14</sup> Clonogenic potential appeared to be largely limited to rare CD19<sup>+</sup> mononuclear cells that were phenotypically distinct from HRS cells.<sup>14</sup>

There was considerable heterogeneity in this clonal cell line; some cells were capable of sustaining tumor growth whereas others had limited clonogenic potential.<sup>14</sup> Interestingly, the cells with clonogenic potential (which might now be regarded as “CSCs”) were phenotypically distinct from the “RS-like” cells. The cells with clonogenic potential were smaller and expressed B-cell markers. Therapeutic implications were not readily apparent at that time, but may in fact exist in light of the growing recognition of the stem cell biology of many cancers including cHL.

The clinical data with rituximab in cHL, including why clinical responses may occur in the absence of CD20 expression on HRS cells, may thus be interpreted in several ways. Depletion of B-cells from tumor masses may lead to apparent shrinkage of the tumor mass without any impact on cells of the malignant clone. Rituximab may potentiate the effects of cytotoxic chemotherapy, perhaps in part by depleting benign B-cells (and hence cytokines and intercellular signals) from the tumor microenvironment.<sup>3</sup> Alternatively, rituximab may target the neoplastic H/RS cell. *The above findings therefore lend support to the possibility that HL arises from malignant stem cells that express B cell markers and that are phenotypically distinct from classic RS cells or their Hodgkin's variants.* This possibility is of interest because of its direct therapeutic relevance, and provides further rationale for the study of rituximab and possibly other B-cell targeted therapies as potential “stem cell inhibitors” in cHL.

### **1.33 Circulating clonotypic B cells as cHL biomarkers**

Whether circulating clonotypic B cells (CCBCs) in cHL represent “CSCs” or a molecularly related population not critical for tumor maintenance or progression is unknown. However, preliminary data from our recently published study of rituximab-ABVD suggest these CCBCs might track with disease status and might have prognostic significance<sup>15</sup>. Based on the above data, our group at Johns Hopkins developed a multicenter, translational phase 2 study of rituximab-ABVD for newly diagnosed, stage II-IV cHL.<sup>15</sup> Of 49 pts, 69% had stage IIB-IV disease; 8% had CD20<sup>+</sup> HRS cells. Rituximab-ABVD was generally well-tolerated with encouraging efficacy, similar to findings from a concurrently published phase 2 study of rituximab-ABVD by the MD Anderson.<sup>12</sup> As these were nonrandomized studies, further clinical trials are needed to define the utility of rituximab in cHL.

In the Johns Hopkins study of rituximab-ABVD, a secondary goal was to assess the behavior of CCBCs clinically. Of the 24 evaluable pts, most (88%) had detectable clonal, surface Ig<sup>+</sup>, CD27<sup>+</sup> ALDH<sup>high</sup> B cells at baseline representing a median of 0.3% of total circulating CD19<sup>+</sup> cells. After rituximab-ABVD, 0/15 pts whose clone disappeared have relapsed vs. 3/6 pts who had persistence or documented reemergence of the clone ( $P = 0.015$ ). This was the first investigation of CCBCs as prognostic markers in HL. Further defining their clinical significance in cHL and the utility of their monitoring is warranted.

## **1.4 Brentuximab vedotin**

The malignant HRS cells in cHL characteristically have strong CD30 expression, whereas normal tissues have limited, restricted expression of CD30. In contrast to earlier generation anti-CD30 therapies,<sup>16</sup> brentuximab vedotin, a monoclonal anti-CD30 antibody-drug conjugate, is highly active in relapsed cHL<sup>17</sup> as well as anaplastic large cell lymphoma.<sup>18</sup> It is an anti-CD30 chimeric monoclonal antibody (cAC10) covalently linked, through an enzyme-cleavable linker, to the anti-tubulin agent MMAE and is FDA approved for relapsed cHL or anaplastic large cell lymphoma. In a pivotal phase 2 study of cHL patients who relapsed after auto BMT, brentuximab vedotin (1.8 mg/kg IV at 3 week intervals, maximum 16 cycles) produced a 75% overall response rate (34% CR rate), with a median time to objective response of 5.7 weeks (range 5.1-56 weeks) and a median time to CR of 12 weeks.<sup>17</sup> This was a heavily pretreated cohort, of whom approximately half did not respond to their most recent systemic therapy.<sup>17</sup> Brentuximab vedotin was associated with a median

response duration of 6.7 months overall, and 20.5 months those who achieved CR. The median PFS was 5.6 months (95% CI, 5.0 – 9.0 months), and the estimated 1-year overall survival (inclusive of patients who received subsequent therapy) was notably 89% (95% CI, 83-95%).

Brentuximab vedotin carried generally manageable toxicities, with the most common including (generally reversible) peripheral neuropathy (mostly sensory) and gastrointestinal side effects.<sup>17</sup> Of the grade  $\geq 3$  toxicities, 8% were from peripheral sensory neuropathy and the majority were hematologic (including 6% grade 4 neutropenia) though without any episodes of febrile neutropenia.<sup>17</sup> The median time to onset of grade 2 peripheral neuropathy was 27.3 weeks (38.0 weeks for grade 3 peripheral neuropathy). Improvement or resolution of neuropathy occurred in 80% of patients. Frontline regimens incorporating brentuximab vedotin are under investigation.

## 1.5 **High-dose therapy in relapsed cHL**

In cHL that relapses after frontline therapy, multiagent salvage chemotherapy, followed by high-dose therapy with auto BMT, is the widely adopted standard, provided that the relapse is chemosensitive. Auto BMT in this setting produces a 1-year FFS of ~70%, a 3-year FFS of ~50%,<sup>19,20</sup> and a significantly better FFS than standard-dose chemotherapy alone.<sup>19</sup> However, *a statistically significant overall survival advantage to auto BMT in cHL has not been demonstrated.*<sup>19,21</sup> Auto BMT also carries a 5-8% mortality risk, a risk of major morbidity, and a nearly 100% risk of infertility. Furthermore, the finding that cHL “CSCs” may circulate even in early-stage disease heightens concern that autograft contamination contributes to relapse.

Given the need for curative but less toxic regimens for relapsed cHL, we conducted a 30-patient pilot study for patients with relapsed chemosensitive cHL and no prior BMT, involving rituximab, high-dose cyclophosphamide *without* BMT, and an allogeneic, GM-CSF producing cancer vaccine.<sup>4</sup> Patients having primary refractory disease or prior BMT were excluded. On preliminary analysis, with median 3.1 year follow-up, the estimated PFS was 70% at 1 year and 61% at 3 years; the estimated overall survival was 91% at 3 years. In patients who had relapsed within 1 year of first-line therapy completion (a poor-risk feature), the estimated PFS was 59%. The regimen was generally well-tolerated. Although late-onset neutropenia (presumably secondary to rituximab) was common, it carried no or no major clinical consequence. All patients who subsequently relapsed were able to proceed to auto or allo BMT. Thus this study had promising results that appear comparable to what would be expected with auto BMT, and significantly, demonstrates that *a clear subset of patients with relapsed chemosensitive cHL could achieve durable remissions with less intensive therapies that do not involve BMT.*

## 1.6 **Summary of hypotheses and design**

Although the clinical utility of rituximab in cHL requires further study, and the data regarding cHL stem cell biology and targeting are preliminary, our present CCBC data suggest that brentuximab vedotin and rituximab are likely to target different cellular compartments in cHL. Brentuximab vedotin, which targets the CD30<sup>+</sup> HRS cells would not be expected to target the CD30<sup>-</sup> clonotypic B-cell population in cHL whereas anti-CD20 therapies such as rituximab might. *This study is based upon the hypothesis that, by targeting different cellular compartments, the combination of anti-CD20 therapy (targeting cHL CSCs) and anti-CD30 therapy (targeting HRS cells and tumor bulk) may be complementary in cHL.* Given the impressive activity of brentuximab vedotin as salvage in the post-transplant setting and the potential for rituximab to target the cHL CSCs, *it is also hypothesize that such an antibody combination alone could be sufficient for patients with first chemosensitive relapse of cHL, allowing high-dose therapy and auto BMT, and the associated major risks, to be avoided.*



This is a single-arm pilot study for first management of relapsed cHL, with 1-year failure-free survival (FFS) as the primary endpoint. This study uniquely investigates the combination of rituximab and brentuximab vedotin to potentially target cHL CSCs and HRS cells, respectively, and uniquely avoids auto BMT (and its associated toxicities) in those patients who have chemosensitive disease. The study aims to investigate the no-BMT intervention only in patients with chemosensitive disease, defined as a response to 4 lead-in doses of single-agent brentuximab vedotin. Responding patients then receive combination brentuximab vedotin plus rituximab, with BMT reserved for treatment failure, whereas patients who do not respond to the brentuximab vedotin lead-in go off-study.

We anticipate that with the rituximab-brentuximab vedotin combination, a significant subset of chemosensitive pts will achieve durable remissions without BMT and that this combination is potentially curative. We also anticipate that, should the combination fail, efficacy of standard salvage regimens will not be compromised, as the mechanism of action of these monoclonal antibodies differs from that of salvage regimens standardly used in this setting (e.g., ifosfamide, carboplatin, etoposide). For similar reasons, hematopoietic stem cell mobilization is unlikely to be impaired. We also expect this approach to be generally well-tolerated with manageable toxicities. Because these patients are not heavily pretreated, and because brentuximab vedotin cycles are capped with mandated adjustments for grade  $\geq 2$  peripheral neuropathy, the incidences of prohibitive neuropathy and neutropenia<sup>17</sup> are expected to be low. Based on previous experiences with rituximab-associated late-onset neutropenia,<sup>22,23</sup> idiopathic late-onset neutropenia is anticipated but should carry no or no major clinical consequence.

As a key secondary endpoint, frequencies of CCBCs (the putative cHL CSC population) will be serially quantified, so as to investigate the potential impact of this approach on cHL CSCs, further characterize the clinical significance of these clonotypic B-cells, and serve as a platform for future studies of cHL CSC targeting.

## **2.0 OBJECTIVES**

### **2.1 Primary objective**

- In patients with chemosensitive relapse of cHL, estimate the probability of 1-year FFS with the combination of brentuximab vedotin and rituximab without high-dose therapy.

### **2.2 Secondary objectives**

- Evaluate circulating clonotypic B cells as potential biomarkers in cHL:
  - Through serial measurements, characterize the impact of the study treatment on the presence and frequency of CCBCs.
  - Characterize the relationship between clonotypic B cell detection and clinical outcome, so as to begin to evaluate CCBC frequencies as potential biomarkers for classification (progression) and risk assessment (PFS) in cHL.
- Describe tolerability, relative delivered dose intensity, and safety including frequency and significance of grade  $\geq 3$  infections and grade  $\geq 3$  late-onset neutropenia.
- Estimate objective response rate (overall response rate, PR, CR) and median times to objective response, best response, and duration of response.
- Estimate probabilities of 1-year and longer-term progression-free, event-free and overall survival, and longer-term FFS.
- Describe disease outcomes according to duration of initial remission.
- Describe disease and survival outcomes with salvage therapy following combination brentuximab vedotin and rituximab, including the probability of freedom from next progression.
- Describe the association between the post-cycle 2 PET result and PFS.
- Descriptively compare FFS with combination brentuximab vedotin and rituximab to FFS

after most recent prior treatment.

### 3.0 **SELECTION OF PATIENTS**

#### 3.1 **Eligibility criteria**

- Age  $\geq 16$  years
- Biopsy-proven diagnosis of cHL (regardless of HRS cell CD20 expression) per the World Health Organization classification criteria<sup>24</sup>; lymphocyte predominant histology is excluded
- Untreated relapse of cHL (with the exception of steroids) as follows:
  - a. HL that relapsed  $\geq 3$  months after completion of first-line chemotherapy or combined modality therapy, and has not yet been treated with salvage chemotherapy
  - b. Stage I-II HL that relapsed  $\geq 3$  months after first-line chemotherapy, then relapsed after radiation therapy delivered with curative intent, and has not yet been treated with salvage chemotherapy
- Radiographically measurable disease ( $\geq 1$  focus of lymphoma measuring  $\geq 1.5$  cm)
- No primary induction failure, defined as failure to achieve CR with first-line chemotherapy or chemoradiation, disease progression during first-line chemotherapy or chemoradiation, or progression or biopsy-proven disease persistence within 8 weeks of first-line therapy completion
- No prior brentuximab vedotin
- If rituximab previously given, lymphoma must have relapsed  $\geq 12$  months after last rituximab dose
- No grade  $\geq 2$  peripheral neuropathy
- No HIV infection, active hepatitis B infection, or active hepatitis C infection
- No receipt of a live vaccine within 4 weeks prior to registration
- Baseline laboratories:
  - a. ANC  $\geq 1000/\mu\text{L}$  and platelets  $\geq 75,000/\mu\text{L}$ , unless due to bone marrow involvement by lymphoma
  - b. Serum creatinine  $\leq 2.0$  mg/dL
  - c. Total bilirubin  $\leq 2.0$  mg/dL (excluding Gilbert's syndrome), unless due to lymphoma
- ECOG performance status 0, 1 or 2.
- No NYHA class III or IV heart disease.
- No active concurrent malignancy with the exception of superficial non-melanoma skin cancer and cervical carcinoma *in situ*.
- Not pregnant or breast feeding; women of childbearing potential and sexually active men must agree to use an accepted and effective method of birth control.
- Signed informed consent.

#### 3.2 **Study interruption or withdrawal**

Potential reasons for interruption or discontinuation of protocol therapy include:

- Serious or intolerable adverse reaction to treatment.
- No response to 4 lead-in doses of single-agent brentuximab vedotin.
- Protocol violation.
- Withdrawal of consent.

### 4.0 **REGISTRATION PROCEDURES**

#### 4.1 **Projected accrual**

Up to 35 patients will be treated and additional patients may be screened and registered, in

order to identify up to 25 patients who are eligible to receive combination brentuximab vedotin and rituximab (those who respond to 4 lead-in cycles of brentuximab vedotin alone) and hence are considered evaluable for the primary endpoint (per Statistical Considerations, Section 9.0). Participation of women and minorities is encouraged.

## **4.2 Registration**

To register a patient at Johns Hopkins, the following documents must be completed and the patient then registered in CRMS:

- Study-specific registration form
- Signed and dated informed consent
- Eligibility checklist

A registration may be cancelled in writing provided that the subject has not begun protocol therapy.

## **5.0 TREATMENT PLAN**

### **5.1 Evaluations and procedures**

Required evaluations are designated in Section 7.0.

### **5.2 Brentuximab vedotin and rituximab**

#### **5.21 Eligibility for antibody combination**

Only patients who have an adequate response to the first 4 cycles of single-agent brentuximab vedotin are eligible to proceed with the combination of brentuximab vedotin and rituximab. A response is considered a) PR or CR per anatomic (CT-based) but not metabolic criteria from the 2007 IWG criteria,<sup>25</sup> or b) stable disease anatomically, with a “negative” PET result by Deauville criteria,<sup>25</sup> per Section 6.1.

If an adequate response is not achieved to 4 cycles of single-agent brentuximab vedotin, the patient will go off study and will be regarded as inevaluable for the primary endpoint and secondary survival endpoints. That patient will, however, be evaluable for the correlative blood work, having a maximum of 3 research blood collections: two at baseline and one at the post-cycle 4 assessment (per Section 7.2).

#### **5.22 Brentuximab vedotin**

Brentuximab vedotin, 1.8 mg/kg IV over 30 minutes (weight capped at 100 kg), is given for up to 10 doses (cycles), with a cycle length of 21 days. Brentuximab vedotin is first given on day 1 of cycles 1, 2, 3, and 4 as a single agent (weeks 0, 3, 6, and 9, respectively). Four cycles are chosen because of the 12-week median time to CR in the pivotal phase 2 trial of brentuximab vedotin after autologous BMT for HL.<sup>17</sup>

Responding patients (per Section 5.21) then receive brentuximab vedotin on day 1 of cycles 5 through 10 (~weeks 12, 15, 18, 21, 24, and 27, respectively) in combination with rituximab as designated in Section 5.23. Any other therapy for lymphoma with the exception of consolidative radiation therapy (RT) is reserved for treatment failure, including BMT.

The designated time points for brentuximab vedotin are +/- 1 day for the first 6 doses of brentuximab vedotin, and +/- 3 days for the remaining doses of brentuximab vedotin.

Brentuximab vedotin is dosed according to actual body weight unless the patient weighs >100 kg, in which case the dose will be calculated based on a 100 kg weight. Premedication for brentuximab vedotin is not routinely administered before the first dose.

Should the patient develop an infusion reaction, premedication with acetaminophen (650 mg p.o.) and diphenhydramine (25 mg p.o. or IV, or 50 mg p.o.) at least 30 minutes before subsequent doses should be given.

### **5.23 Rituximab**

Rituximab 375 mg/m<sup>2</sup> IV (may be rounded to the nearest 100 mg) is given for up to 8 “induction” doses: day 1 of week 12, 13, 14, and 15, then day 1 of week 18, 21, 24, and 27. This is followed by rituximab “maintenance” (375 mg/m<sup>2</sup> IV once every 3 months x 2 doses) to complete a ~ 1 year total course of therapy.

The designated time points for rituximab are +/- 1 day for the first 4 doses, +/- 3 days for the next 4 doses of rituximab, and +/- 1 week for the remaining two doses given as maintenance.

Rituximab is dosed according to actual body weight. The rituximab dose may be split over 2 days in the case of significant infusion reaction.

Rituximab is initially given in 1 week intervals with the intent of maximizing B-cell depletion early in the treatment course. Maintenance rituximab is given with the intent of facilitating CSC targeting after reduction in tumor bulk.

### **5.24 Dose modifications and delays**

The dose of rituximab is never adjusted. Dose reductions in brentuximab vedotin may be required as outlined below.

#### **1) Dose modifications for hematologic toxicities**

The dose of rituximab is never adjusted, though may be split over 2 days in the case of significant infusion reaction. Should grade 4 neutropenia occur despite growth factor support and not resolve by 7 days, brentuximab vedotin is to be reduced to 1.2 mg/kg, or if already at 1.2 mg/kg, then to 0.9 mg/kg. Should grade 4 neutropenia occur despite these measures and be accompanied by grade  $\geq 3$  infection, continuation with study treatment shall be discussed with the PI and a decision rendered on a case-to-case basis.

For grade 4 thrombocytopenia not attributable to bone marrow involvement by lymphoma or another cause, brentuximab vedotin is to be reduced to 1.2 mg/kg, or if already at 1.2 mg/kg, then to 0.9 mg/kg. Should grade 4 thrombocytopenia occur despite these measures, and not be adequately supported by platelet transfusion, continuation with study treatment shall be discussed with the PI and a decision rendered on a case-to-case basis.

There will be no dose modifications or delays for anemia.

#### **2) Dose delays for hematologic toxicities**

Should neutropenia occur, the next dose of study drug(s) must be delayed until the ANC is  $\geq 1000/\mu\text{L}$  unless the neutropenia is attributable to bone marrow involvement by lymphoma. Should grade 4 thrombocytopenia occur that is not attributable to bone marrow involvement by lymphoma, the next dose of study drug(s) must be delayed until the thrombocytopenia is  $< \text{grade } 4$ , without platelet transfusion in the preceding 3 days. Anemia or thrombocytopenia should be managed per institutional guidelines and transfusion considered as necessary. Study drug(s) may be delayed as appropriate for grade  $\geq 3$  infection or as otherwise deemed medically necessary.

**3) Dose modifications and delays for neuropathy**

In the case of grade 2 peripheral neuropathy, reduce brentuximab vedotin to 1.2 mg/kg IV and resume treatment without delay; or, if at 0.9 mg/kg IV when grade 2 neuropathy occurs, continue dosing at that level.

For grade 3 peripheral neuropathy, hold brentuximab vedotin until the toxicity is  $\leq$  grade 2, then reduce to 0.9 mg/kg IV and resume treatment. If already at 0.9 mg/kg, discontinue brentuximab vedotin.

For grade 4 peripheral neuropathy, brentuximab vedotin must be discontinued. Decisions to continue on study will be made on a case-by-case basis with the PI.

**4) Treatment should hepatitis B virus reactivate**

Should HBV reactivate during study treatment, immediately and permanently discontinue rituximab and institute antiviral treatment (see Section 5.32). Further decisions regarding study participation will be made on a case-by-case basis.

**5) Combination therapy and correlative studies during treatment delays**

Should brentuximab vedotin be delayed due to toxicity, the first 4 weekly doses of rituximab begun with Cycle 5 should continue on schedule (provided above hematologic criteria are met). Subsequent doses of rituximab that are due to be given concurrently with brentuximab vedotin (e.g., originally weeks 18, 21, 24, and 27) and may be delayed up to 10 days, beyond which rituximab and brentuximab vedotin may be given on separate days. Any correlative blood draws (for CSC assays) due at the time a treatment is delayed, will be coupled with the new schedule of rituximab.

**5.3 Supportive care**

Supportive care including but not limited to antiemetics, antibiotic prophylaxis, infection management and transfusion support shall be delivered according to good medical practice and institutional standards.

**5.31 Filgrastim**

The use of growth factors for neutropenia management is left to the discretion of the treating physician and will be tracked.

**5.32 Hepatitis B infection**

All patients must be screened for HBV infection, per Section 7.0, before initiating study treatment. For patients having evidence of prior HBV infection, consult with a specialist regarding monitoring and consideration of antiviral therapy.

Monitor patients with prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during, and for several months following, rituximab therapy. HBV reactivation has been reported up to 24 months following therapy completion.

In patients who develop reactivation of HBV while on study, immediately discontinue rituximab and institute appropriate treatment. Insufficient data exist regarding the safety of resuming rituximab in patients who develop HBV reactivation.

**5.4 Other lymphoma therapies****5.41 Permitted lymphoma therapies**

With the exception of consolidative RT and, if medically necessary, steroids, **no other**

**treatment for lymphoma is permitted on study in the absence of treatment failure or an event that leads to study withdrawal.**

#### **5.42 Radiation therapy**

Consolidative RT is permitted for relapse that has been localized, *after* completion of the full planned combination of brentuximab vedotin-rituximab (i.e., through cycle 10) and associated responsive assessment and research blood draws. RT may then be given, either prior to or concurrently with maintenance rituximab. RT records (including summary of fields, dose, technique) will be obtained and toxicities during RT tracked as they may related to the study drugs. Guidelines for consolidative RT are provided in the Appendix.

#### **5.43 Steroids**

Steroids are permitted if medically necessary, for short-term use in lymphoma treatment (in urgent situations only; no longer-term use) or otherwise as medically necessary. Their use will be tracked.

### **5.5 Correlative studies**

Blood will be collected for correlative studies on cHL CSC biology (i.e. frequencies of circulating clonotypic B cells) per Section 7.2. These correlative blood draws are required. The assays will be performed in the Jones laboratory at Johns Hopkins, based on previously published methods.<sup>2</sup> Specimens will be banked for future related research on cHL stem cell biology and biomarkers.

### **5.6 Follow-up procedures**

The minimum follow-up for study purposes is specified in Section 7.0. Standard monitoring, consisting of an exam and indicated diagnostic studies is suggested at these or more frequent intervals according to good medical practice.

Should disease progression occur despite combination brentuximab vedotin-rituximab, information that will be tracked includes but is not limited to the following unless patient consent is withdrawn: frequency of circulating clonotypic B cells, type of salvage regimen(s) including hematopoietic BMT, freedom from next progression, overall survival and all-cause mortality. Copies of relevant medical records will be obtained.

### **5.7 Toxicity grading and reporting**

Toxicities are graded according to the National Cancer Institute (NCI) Common Toxicity Criteria, version 4.0 and attribution to study treatment designated. Toxicities will be reported in accordance with IRB, federal, and sponsor-specified requirements.

In those cases where the NCI criteria do not apply, intensity will be defined as:

Mild: awareness of symptom or sign, but easily tolerated

Moderate: discomfort is enough to cause interference with normal activities

Severe: inability to perform normal daily activities

Life threatening: immediate risk of death from the reaction as it occurred

Specific adverse event grading and reporting requirements for rituximab are designated in Appendix C.

## **6.0 MEASUREMENT OF EFFECT**

### **6.1 Response assessment**

Response assessment is based on the 2007 revised IWG criteria for lymphoma<sup>25</sup> and the

Deauville criteria<sup>26,27</sup> as follows (see <sup>18</sup>F FDG PET evaluation form, Appendix).

Post-cycle 10 (or last cycle) response assessment and subsequent assessments utilize the 2007 revised IWG criteria for lymphoma.<sup>25</sup>

Post-cycle 4 (interim) response assessment utilizes the CT-based but not metabolic criteria from the 2007 revised IWG criteria for lymphoma, as these metabolic criteria were not developed for interim scans.<sup>25</sup> In addition, the interim and post-cycle 10 (or last cycle) metabolic imaging is evaluated with the Deauville criteria<sup>26,27</sup> (“negative” = score of 1, 2, or 3; “positive” = score of 4 or 5).

Up to two expert radiologists will be assigned to interpret these and potentially other imaging results for study purposes.

For exploratory purposes only, characterization of the intensity of FDG uptake using semiquantitative methods is planned (e.g., delta SUV<sub>max</sub>,<sup>28</sup> PERCIST<sup>29</sup>).

## 6.2 **Disease and survival endpoints**

**6.21 Progression-free survival** (PFS) is defined as the interval from treatment initiation to the date of first objective disease progression or relapse, death from any cause, or last patient evaluation. Patients who have not progressed, relapsed or died will be censored at the last date they were assessed.

**6.22 Failure-free survival** (FFS) is defined as the interval from treatment initiation to the date of first objective disease progression or relapse; documented failure to achieve CR by the time of post-cycle 8 assessment; death from any cause; or last patient evaluation. Patients without treatment failure will be censored at the last date they were assessed and deemed failure-free.

**6.23 Event-free survival** (EFS) is defined as the interval from treatment initiation to any treatment failure (per Section 6.22), discontinuation of specified treatment due to any reason (e.g., toxicity, patient or physician preference, initiation of alternative treatment without documented treatment failure), death from any cause, or last patient evaluation. Patients without an event will be censored at the last date they were assessed.

**6.24 Overall survival** (OS) is defined as the interval from protocol-specified treatment initiation to the date of death from any cause or last patient contact. Surviving patients will be censored at the date they were last known to be alive.

**6.25 Time to tumor progression** (TTP) is defined as the interval from the date the patient was last found to be progression-free, to the date of first objective disease progression.

## 6.3 **Dose intensity**

The delivered relative dose intensity of brentuximab vedotin and rituximab will be calculated per standard published methods.<sup>30</sup> If the patient does not complete 8 cycles of therapy, the projected duration of 8 cycles will be regarded as the reference time.

## 7.0 **STUDY PARAMETERS**

The tables in Sections 7.1 and 7.2 below summarize the minimum evaluations required for

study purposes in the absence of subsequent relapse/progression. This does not include all assessments indicated as standard of care, the results of which may be collected and used for study purposes.

## 7.1 Core clinical evaluations

Required clinical evaluations						
	Baseline <sup>a</sup>	0-5 d before each cycle	0-5 d before C5	0-5 d before C7 and C9	3-4 weeks after C10 <sup>e</sup>	Q3 mo x 1 y, then Q6 mo x 3 y <sup>f</sup>
History & physical	X	X			X	X
Pathology review <sup>b</sup>	X					
CBC with differential	X	X			X	X
Chemistry panel <sup>h</sup>	X	X			X	X
HIV antibody	X					
Hepatitis B testing <sup>k</sup>	X					
Hepatitis C antibody	X					
Pregnancy test <sup>i</sup>	X					
Bone marrow biopsy	X				X <sup>g</sup>	
<sup>18</sup> F FDG PET-CT <sup>c, d, j</sup>	X		X		X	
CT chest-abd-pelvis <sup>c, j</sup>				X		X

<sup>a</sup> Baseline scans must be performed within 3 weeks prior to start of treatment; remaining baseline evaluations must be performed within 4 weeks, except for bone marrow biopsy which is within 8 weeks. Standard-of-care assessments that were performed before registration may be used for protocol purposes. Include start and stop dates for prior lymphoma therapy, if available, and type of therapy.

<sup>b</sup> Including tumor EBV status and HRS cell CD20 expression, both designated as present or absent.

<sup>c</sup> With bidimensional tumor measurements. Add neck CT if clinically indicated.

<sup>d</sup> Including additional, dedicated contrast-enhanced CT (omit iodinated IV contrast if contraindicated).

<sup>e</sup> Prior to any RT or maintenance rituximab. Should 10 cycles not be completed, then ~3-4 weeks after last protocol-specified therapy, prior to any RT or maintenance rituximab.

<sup>f</sup> Measured from post-cycle 10 evaluation (includes required assessment prior to each dose of maintenance rituximab). Designated time points are +/- 1 week.

<sup>g</sup> If involved with lymphoma at baseline.

<sup>h</sup> Chemistry panel includes BUN, creatinine, AST, ALT, total bilirubin, alkaline phosphatase.

<sup>i</sup> Serum or urine HCG in females of childbearing potential.

<sup>j</sup> It is preferred that PET/CT scans be done at the same facility. Baseline, post Cycle 4, and post cycle 10 (or last cycle) CT and PET/CT scans, if performed elsewhere, must be submitted for Johns Hopkins review.

<sup>k</sup> HBsAg, anti-HBc, and anti-HBs. For patients with risk factors or prior hepatitis B infection, add e-antigen. If hepatitis B infection screen is positive, monitor viral load and consult with specialist (Section 5.32).



## 7.2 **Research blood collections**

<b>Required research blood draws</b>		
<b>Time Point <sup>a, b</sup></b>	<b>Sample Type</b>	<b>Amount</b>
1-4 weeks before study treatment	Heparin SST	Seven 10 mL tubes One 7 mL tube
D1 C1 of BV	Heparin SST	Five 10 mL tubes One 3 mL tube
D1 of C5, C7, and C9	Heparin SST	Five 10 mL tubes One 3 mL tube
3-4 weeks after C10 <sup>c</sup>	Heparin SST	Seven 10 mL tubes One 3 mL tube
Prior to each maintenance rituximab	Heparin SST	Five 10 mL tubes One 3 mL tube
Every 6 months x 2, following last maintenance rituximab	Heparin SST	Five 10 mL tubes One 3 mL tube
Upon next relapse/progression <sup>d</sup>	Heparin SST	Five 10 mL tubes One 3 mL tube

<sup>a</sup> Research labs must be drawn 0-3 days prior to any scheduled treatment up through C9; with maintenance rituximab, the window is 0-5 days prior.

<sup>b</sup> Patients who relapse/progress will have measurements up to and including the time of relapse/progression.

<sup>c</sup> Prior to consolidative radiation therapy or maintenance rituximab; or should 10 cycles not be completed, then ~3-4 weeks after last protocol-specified therapy, prior to any RT or maintenance rituximab.

<sup>d</sup> When feasible.

## 8.0 **DRUG INFORMATION**

### 8.1 **Rituximab**

#### Other names

IDEC-C2B8, Rituxan.

#### Classification

Monoclonal antibody.

#### Mode of action

This chimeric mouse/human anti-CD20 antibody binds human complement and causes lysis of B-cells. It has significant activity in assays for antibody dependent cellular cytotoxicity.

#### Storage and stability

Stored at 2-8° C. Reconstituted antibody is stable for 24 hours upon refrigeration followed by 12 hours at room temperature.

#### Preparation

Diluted with normal saline to a concentration of 1 - 4 mg/mL. Shaking can cause

aggregation and precipitation of the antibody and should be avoided.

#### Administration and infusion reactions

Intravenous infusion. The initial dose rate should be 50 mg/hour for the first hour. If no toxicity is seen, the dose rate may be escalated gradually to a maximum of 400 mg/hour. Subsequent doses have required much less infusion time. If the first dose of rituximab is well tolerated, the starting flow rate for subsequent doses is 100 mg/hour, then increased gradually (e.g., 100 mg/hour increments at 30-minute intervals) not to exceed 400 mg/hour. Alternatively, subsequent doses (but not the first rituximab dose) may be given as a rapid infusion in accordance with institutional standards (e.g., 20% of total dose over 30 minutes, followed by 80% of total dose over 60 minutes), provided there was no severe reaction to the previous dose of rituximab.

Patients may experience infusion reactions. When these occur, the antibody infusion should be temporarily discontinued or slowed. When symptoms improve, the infusion should be resumed, initially at half the previous rate. Following the antibody infusion, the intravenous line should be kept open for medications, as needed. If there are no complications, the intravenous line may be discontinued after one hour of observation.

Oral premedication (acetaminophen and diphenhydramine hydrochloride) may be administered 30 to 60 minutes prior to starting each infusion of rituximab. Steroid premedication is permitted in the case of prior infusion reaction. Since transient hypotension may occur during rituximab infusion, consideration should be given to withholding antihypertensive medications 12 hours prior to rituximab infusion.

#### Availability

Commercially available in 10 mL (100 mg) and 50 mL (500 mg) single-use vials at a concentration of 10 mg /mL.

#### Incompatibilities

Do not mix or dilute rituximab with other drugs. No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed.

#### Side effects of rituximab include:

1. Infusion related symptoms: Fevers, chills, rigors, hypotension, anaphylaxis or hypersensitivity reactions, arrhythmia, dyspnea, bronchospasm and angioedema. In rare cases (0.04-0.07%), severe and fatal cardiopulmonary events, including hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, and cardiogenic shock, have occurred, nearly all in association with the first infusion. Patients with preexisting cardiac conditions, including arrhythmia and angina, have had recurrences of these cardiac events during rituximab infusions.
2. Gastrointestinal: Nausea, vomiting.
3. Hematologic: Leukopenia, anemia, thrombocytopenia. In clinical trials, NCI CTC Grade 3 and 4 cytopenias were reported in 48% of patients treated with rituximab, including lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). In addition, prolonged pancytopenia, marrow hypoplasia, and late-onset grade 3 and 4 neutropenia<sup>23</sup> have occurred. The late-onset neutropenia may be GCSF responsive.

4. **Dermatologic:** Rash, pruritus, urticaria, and rarely severe mucocutaneous reactions.
5. **Infectious:** Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of rituximab-based therapy. Infections have been reported in some patients with prolonged hypogammaglobulinemia (defined as hypogammaglobulinemia >11 months after rituximab exposure). New or reactivated viral infections included cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C. Discontinue rituximab for serious infections and institute appropriate anti-infective therapy. Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, has occurred in patients treated with drugs classified as CD20-directed cytolytic antibodies, including rituximab. Cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation also has occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative, anti-HBc positive and hepatitis B surface antibody [anti-HBs] positive). HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis. The median time to the diagnosis of hepatitis was approximately four months after the initiation of rituximab and approximately one month after the last dose.  
 JC virus infection resulting in Progressive multifocal leukoencephalopathy (PML) and death can occur in rituximab-treated patients with hematologic malignancies or with autoimmune diseases. The majority of patients with hematologic malignancies diagnosed with PML received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. The patients with autoimmune diseases had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their last infusion of rituximab. Consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Discontinue rituximab and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.
6. **Renal and electrolyte:** Renal toxicity has occurred in patients with high numbers of circulating malignant cells ( $>25,000/\text{mm}^2$ ) or high tumor burden who experience tumor lysis syndrome. Although rare, tumor lysis syndrome has been reported in postmarketing studies and is characterized in patients with a high number of circulating malignant cells ( $>25,000/\text{ul}$ ) by rapid reduction in tumor volume, renal insufficiency, hyperkalemia, hypocalcemia, hyperuricemia, and hyperphosphatemia
7. **Other:** Headache, asthenia. The following immune serious adverse events have been reported to occur rarely ( $<0.1\%$ ) in patients following completion of rituximab infusions: arthritis, disorders of blood vessels (vasculitis, serum sickness and lupus-like syndrome), lung disorders including pleuritis and scarring of the lung (bronchiolitis obliterans), eye disorders (uveitis and optic neuritis), and severe bullous skin reactions (including toxic epidermal necrolysis and pemphigus) that may result in fatal outcomes. Patients may have these symptoms alone or in combination with rash and polyarthritis

## 8.2 **Brentuximab vedotin**

### Other names

Adcentris™, SGN-35

### Classification

Antibody-drug conjugate

### Mode of action

Brentuximab vedotin is an antibody-drug conjugate consisting of a CD30 targeted chimeric monoclonal antibody (cAC10) covalently linked, via an enzyme-cleavable linker, to the anti-tubulin agent MMAE. cAC10 has a typical structure of the human IgG1 subclass.

### Storage and stability

Vials must be stored under refrigeration at 2-8°C. Chemical and physical stability of the reconstituted brentuximab vedotin drug product has been demonstrated for 24 hours at 2-8°C and 25°C. However, brentuximab vedotin does not contain preservatives; therefore, from a microbiological standpoint, opened and reconstituted vials should be used immediately. If not used immediately, the in-use storage should not be longer than 24 hours under refrigeration at 2-8°C. It is recommended that brentuximab vedotin vials and solutions be protected from direct sunlight until the time of use.

### Preparation

Brentuximab vedotin is a sterile, preservative-free, white to off-white lyophilized cake or powder, supplied in single-use vials. Each vial contains brentuximab vedotin, trehalose, sodium citrate, and polysorbate 80. Brentuximab vedotin drug product is reconstituted with Sterile Water for Injection. The pH of reconstituted product is approximately 6.6.

The reconstituted brentuximab vedotin drug product is a clear to slightly opalescent, colorless solution with no visible particulate matter. The reconstituted solution is subsequently diluted in sterile 0.9% Sodium Chloride for Injection, USP, 5% Dextrose Injection USP, or Lactated Ringer's Injection USP, for IV administration.

### Administration and infusion reactions

Administered as an IV infusion over 30 minutes. Infusion-related reactions may occur during or soon after brentuximab vedotin treatment. Symptoms include chills, nausea, cough, itching, and shortness of breath. Serious allergic reaction (including wheezing, difficulty breathing, hives, itching, swelling) that requires immediate medical attention and treatment discontinuation is possible. Premedication is not routinely given with the first dose of brentuximab vedotin, but is advised (e.g., diphenhydramine, acetaminophen) for subsequent doses should an infusion-related reaction occur.

### Potential drug interactions

Evidence in humans suggests brentuximab vedotin and MMAE are neither inhibitors nor inducers of CYP3A4. Data indicate that MMAE is a substrate of CYP3A4. No dose adjustment should be necessary based on co-administration of a CYP3A4 inducer. Patients receiving strong CYP3A4 inhibitors concomitantly with brentuximab vedotin should be closely monitored for AEs.

### Distribution, metabolism and excretion

The distribution of brentuximab vedotin when administered intravenously at standard doses is primarily limited to the vascular space. The primary route of excretion of MMAE is fecal, whereas urinary excretion is moderate, with data suggesting a low propensity for metabolism-based biotransformation.

Side effects of brentuximab vedotin

The table below is adapted from Comprehensive Adverse Event and Potential Risks (CAEPR) list of reported and/or potential AEs associated with brentuximab vedotin. Other toxicities may occur, and brentuximab vedotin in combination with other agents could exacerbate AEs or cause AEs not previously reported with either agent.

<b>Adverse Events with Possible Relationship to Brentuximab Vedotin (CTCAE 4.0 Term) [n= 249]</b>		
<b>Likely (&gt;20%)</b>	<b>Less Likely (&lt;=20%)</b>	<b>Rare but Serious (&lt;3%)</b>
<b>BLOOD AND LYMPHATIC SYSTEM DISORDERS</b>		
	Anemia	
<b>GASTROINTESTINAL DISORDERS</b>		
	Constipation	
Diarrhea		
Nausea		
	Vomiting	
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>		
	Chills	
	Edema	
Fatigue		
Fever		
	Infusion related reaction	
<b>IMMUNE SYSTEM DISORDERS</b>		
		Anaphylaxis
<b>INFECTIONS AND INFESTATIONS</b>		
	Upper respiratory infection	
<b>INVESTIGATIONS</b>		
Neutropenia <sup>2</sup>		
	Thrombocytopenia	
	Leukopenia <sup>2</sup>	
<b>METABOLISM AND NUTRITION DISORDERS</b>		
	Anorexia	
		Tumor lysis syndrome
<b>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</b>		
	Arthralgia	
	Back pain	
	Myalgia	
<b>NERVOUS SYSTEM DISORDERS</b>		
	Dizziness	

<b>Adverse Events with Possible Relationship to Brentuximab Vedotin (CTCAE 4.0 Term) [n= 249]</b>		
<b>Likely (&gt;20%)</b>	<b>Less Likely (&lt;=20%)</b>	<b>Rare but Serious (&lt;3%)</b>
	Headache	
		Other nervous system disorders (PML)
	Peripheral motor neuropathy	
Peripheral sensory neuropathy		
<b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b>		
	Cough	
	Dyspnea	
		Pneumonitis <sup>1</sup>
<b>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</b>		
	Alopecia	
	Pruritus	
	Rash (maculopapular)	
		Stevens-Johnson syndrome

<sup>1</sup>Elevated risk of pulmonary toxicity (e.g., pneumonitis) has been observed in patients treated with brentuximab vedotin in combination with bleomycin.

<sup>2</sup>Thus may increase the risk of infection, including severe infection.

**Note:** Patients who are pregnant or breastfeeding should not receive brentuximab vedotin because of potential risk to the fetus or nursing baby.

## 8.2 **Toxicity grading and reporting**

Toxicities are graded according to the National Cancer Institute (NCI) Common Toxicity Criteria, version 4.0 and attribution to study treatment designated. Toxicities will be reported in accordance with IRB requirements.

In those cases where the NCI criteria do not apply, intensity will be defined as:

Mild: awareness of symptom or sign, but easily tolerated

Moderate: discomfort is enough to cause interference with normal activities

Severe: inability to perform normal daily activities

Life threatening: immediate risk of death from the reaction as it occurred

## 9.0 **STATISTICAL CONSIDERATIONS**

### 9.1 **Primary endpoint**

#### 9.11 **Definition of primary endpoint**

This is a single-arm pilot study with 1-year FFS as the primary efficacy measure and endpoint. A failure is defined as relapse/progression, lack of CR by completion of brentuximab vedotin + rituximab "induction" (post-cycle 10 assessment), or death. Overall

hazard rate estimates and 95% confidence intervals (CIs) as well as non-parametric Kaplan-Meier estimates will be used to estimate FFS, and the 1-year FFS reported with 95% CI. The design includes interim analyses for futility.

### **9.12 Sample size**

Based in part on projected accrual, up to 25 patients eligible to receive combination brentuximab vedotin-rituximab, as determined after 4 cycles of single-agent brentuximab vedotin, will be accrued and considered evaluable for the primary efficacy measure. Up to 35 may begin treatment with single-agent brentuximab vedotin to identify those eligible for the antibody combination, as not all patients are expected to respond to brentuximab vedotin. Only those patients who receive the antibody combination will be considered evaluable for the primary endpoint.

The 1-year FFS will be compared to a reference of 40% (hazard rate = 0.916/person-year, i.e. median of 9.08 months). In patients with first chemosensitive relapse of cHL, a 1-year FFS of 70% is a reasonable benchmark for what one could expect with BMT. However, because this study aims to avoid BMT and its associated toxicities, a 1-year FFS of 60% (hazard rate = 0.51/person-year, median of 16.3 months) would be considered promising and is the benchmark for this study. Assuming exponential survival, accrual of ~8 evaluable (chemosensitive) patients per year, minimum 1 year of additional follow-up and a two-sided alpha of 0.10, the sample size of 25 will have 83% power to detect a hazard ratio of 0.55.

## **9.2 Early stopping guidelines**

### **9.21 Early stopping rules for futility**

The operating characteristics of design are demonstrated by simulations, carried out with exponential survival and staggered patient entry. The design assumes a sample size of 25 evaluable patients and the above accrual period and additional follow up. The null 1-year FFS is 40%. We have designed the study to stop early only if the posterior probability of 1-year FFS being less than the null is 80% or higher.

Interim analyses begin once 10 evaluable patients have been entered and occur after groups of 5 patients thereafter up to a maximum of 25. The interim analysis estimates of 1-year FFS are based on analyses with an underlying Dirichlet process prior. We approximate the posterior distribution, which is actually a mixture of Beta distributions, the mixture depending on the amount of censoring, with a single Beta distribution. The parameters of this posterior Beta distribution are based on the number of failures and the effective sample size at one year, combined with the parameters of the prior.

The following table summarizes the operating characteristics of the futility stopping rule under various scenarios for the underlying exponential FFS, based on 1000 simulations. For futility monitoring we optimistically characterize the uncertainty of the 1-year FFS estimate with the prior:  $\text{beta}(3,2)$ . This implies that our prior guess at the 1-year FFS in this study is 60% and there is 90% certainty that the 1-year FFS is between 25% and 90%.

<b>Characteristics of futility stopping rule with N of 25</b>						
1-y FFS	Prob Stop for Futility	Avg N	Estimated 1-y FFS	lo 95% Post Int'l	hi 95% Post Int'l	Prob H0 Rejected
0.10	1.00	10	0.10	0.00	0.30	0.00
0.20	1.00	10	0.20	0.00	0.40	0.00
0.30	0.98	11	0.28	0.00	0.47	0.01
<b>0.40</b>	<b>0.84</b>	<b>14</b>	<b>0.37</b>	<b>0.10</b>	<b>0.60</b>	<b>0.10</b>
0.50	0.59	17	0.45	0.20	0.68	0.30
0.60	0.27	22	0.57	0.30	0.76	0.66

## 9.22 Early stopping rules for safety

If it becomes evident that the proportion of patients who develop grade 4 infection (up through 6 months following completion of study-specified treatment) convincingly exceeds 10%, the study will be halted for a safety consultation. Only patients who receive combination brentuximab vedotin-rituximab will be considered evaluable for this safety stopping rule, with censoring for this toxicity upon treatment of subsequent relapse/progression. The stopping rule will hold enrollment if the posterior probability of this toxicity more than 0.10 is 75% or higher. The prior for this monitoring rule is beta(1,9). This means that our prior guess at the proportion with grade 4 infection is 10%, and there is 90% probability that this proportion is between 0.57% and 28.3%.

The following table shows the resulting stopping rule. For example, the rule will call for stopping the study if 3 out of the first 9 evaluable patients experience a grade 4 infection. The next shows the percent of the time that the stopping rule will terminate the study under different hypothetical risks of grade 4 infections, along with the average sample size at time of stopping (based on 5000 simulations).

<b>Stopping rule for grade 4 infection</b>			
Study paused if:	2 AEs	3 AEs	4 AEs
And number of patients between:	2 - 8	9 - 16	17 - 25

The next table shows the percent of the time that the stopping rule will terminate the study under different hypothetical risks of grade 4 infections, along with the average sample size at time of stopping (based on 5000 simulations).

<b>Operating characteristics of safety stopping rule based on 5000 simulations</b>		
True Risk	Prob. Stopping	Avg. N
0.02	1.1%	24.8
0.05	8.6%	23.7
0.10	34.0%	20.2
0.15	62.2%	16.1
0.20	81.6%	12.5
0.25	92.0%	9.9
0.30	98.0%	7.7

## 9.3 Secondary endpoints

### 9.31 Correlative studies of CCBCs

A key secondary objective, through serial measurements of CCBC frequencies, is to characterize the impact of the study treatment on the presence and frequency of CCBCs,



and to investigate the clinical utility of CCBC assays in cHL. Specifically, the study begins to evaluate CCBCs as potential biomarkers for classification (progression) and risk assessment (PFS) in cHL. It is hypothesized that CCBC assays could be useful as a classification biomarker (their persistence might increase the probability of progression) and risk assessment biomarker (their persistence might correlate with inferior PFS).

It is expected that 90% of patients will have detectable CCBCs at baseline and therefore our projected sample size for correlative endpoints is 22. The following analyses are planned:

### **1) Trends in CCBC frequencies**

Changes in CCBC frequencies will be displayed for each patient (baseline to post-cycle 4 brentuximab vedotin and subsequent changes with rituximab-brentuximab vedotin treatment) and trends assessed with descriptive summary statistics of raw, transformed continuous and binary (proportion with clearance) data. A regression line with the estimated slope for log CCBC values may be calculated individually and an overall mean slope reported. The exact analytic plan may vary depending of the results of serial CCBC measurements, but patients will be categorized as having CCBC decline (clearance) or CCBC increase (persistence). If changes occur gradually over the duration of study treatment for most patients and appear linear, the slope from simple linear regression models will be used to evaluate CCBC changes. If clearance is early and complete for a proportion of patients, regression analyses will not be necessary. If the decline in CCBCs extends past the period of combination treatment, a second binary indicator will be considered.

### **2) Classification biomarkers for progression**

Sensitivity and specificity of CCBC changes for relapse/progression will be estimated:

a) To evaluate more immediate effects on disease status, we will construct tables indicating presence or absence of progression within a given time period, relate this to preceding categorical changes in CCBCs, test these associations with Fisher's exact tests and estimate sensitivity, specificity and positive and negative likelihood ratios.

b) To evaluate longer-range effects, a linear regression (or simple difference) will estimate each patient's CCBC changes during rituximab-brentuximab vedotin, with pts then grouped according to sign of the slope (positive or negative). The proportion progressing by 1 y and 2 y will be estimated and compared using a Fisher's exact test. Congruence of CCBC changes and ultimate clinical outcome will also be itemized on a case-by-case basis, with the proportion of congruent cases (CCBC clearance and remission, or CCBC persistence and relapse) and non-congruent cases reported with 95% CIs.

#### **Implications of sample size for estimating sensitivity and specificity**

With an N of 22, with a binary predictor for progression and 50% progression rate, sensitivity and specificity could be estimated with a 95% CI of +/- 0.3; likelihood ratios for combinations of sensitivity and specificity are shown in the table below.

Likelihood ratios with N of 22 and 50% progression rate			
Sens.	Spec.	LR+ (95% CI)	LR- (95% CI)
60%	60%	1.50 (0.63-3.58)	0.67 (0.28-1.59)
70%	70%	2.33 (0.87-6.23)	0.43 (0.16-1.14)
80%	80%	4.00 (1.18-13.53)	0.25 (0.07-0.85)

Implications of sample for a Chi-square test

If there are approximately equal numbers of patients with clearance of CCBCs compared to the number of patients with persistence, and our hypotheses are correct, we could expect large differences in the probability of progression between these groups. If the expected proportion of patients that progress with complete clearance is very low, 5%, and if the expected proportion of patients that progress with persistence or increasing CCBCs is large, 50%, a sample size of 22 (11 per group) with a two-sided 0.10 Chi-square test would provide 84% power to detect this 45 % difference (0.05 vs 0.50).

**3) Risk assessment biomarkers for PFS**

Even if CCBCs do not have high sensitivity and specificity for the classification of patients at risk for progression, we expect that CCBCs may be useful as a risk assessment biomarker. Patients with persistence of CCBCs would be expected to have shorter durations of PFS. As in correlative analysis 2b, patients will be grouped by CCBC changes and Kaplan-Meier curves for PFS generated, to evaluate any potential association between CCBC persistence and shorter PFS.

Implications for a sample size of 22 for the hazard ratio

In evaluating CCBCs as a risk assessment biomarker for PFS, the sample size calculations are based on using a binary predictor, assuming exponential survival, and varying proportions of patients in the group with persistent or increasing CCBCs (and thus an expected worse prognosis). If Group 1 indicates patients with persistent or increasing CCBCs and Group 2 indicates patients with CCBC clearance, the table below shows the power for a minimum detectable effect (HR; G1/G2) of 4.0 at the end of 3 years. G1 and G2 event rates of 1.0 and 0.25 per person-year (HR 4.0), corresponding to median PFS times of 8.35 and 33 months, 3-y accrual and 1-y additional follow-up were assumed.

Power to detect HR for PFS				
N	% G1 (n1/n2)	HR (G1/G2)	Power (3-y)	Power (4-y)
22	0.27 (6/16)	4.0	0.71	0.78
22	0.50 (11/11)	4.0	0.84	0.88
22	0.73 (16/6)	4.0	0.81	0.85

**9.32 Secondary clinical endpoints**

- 1) The frequencies of toxicities by type and grade will be described by tabulation and reported with exact 95% binomial CI's. These include but are not limited to grade  $\geq 2$  peripheral neuropathy, grade  $\geq 3$  infection and grade  $\geq 3$  hematologic toxicities including late-onset neutropenia. Duration, GCSF responsiveness, and clinical consequence of late-onset neutropenia will be described.  
Delivered relative dose intensity of brentuximab vedotin and rituximab will be summarized with the mean, median, minimum and maximum values and interquartile range.
- 2) Objective response rates (CR+PR, CR, PR) and median times to response, best response, and duration of response will be reported, with appropriate estimates and 95% CIs.
- 3) One year and longer term failure-free, progression-free, event-free and overall survival will be reported using non-parametric KM estimates and 95% CIs.
- 4) Disease outcomes will be described separately for patients who relapsed  $\leq 1$  year or  $>$

- 1 year after completion of first-line chemotherapy or chemoradiation.
- 5) Disease outcomes will be reported according to the post-cycle 4 PET scan result (negative vs. positive) using the Kaplan Meier method and 95% CI.
- 6) Descriptive statistics will be used: proportions, mean (std), median (range) and Kaplan-Meier estimates to describe disease and survival outcomes with salvage therapy following rituximab- brentuximab vedotin, including the probability of freedom from next progression.
- 7) For comparison of FFS with brentuximab vedotin-rituximab to FFS after most recent prior treatment, landmark analyses will be used for each of these endpoints separately and the median FFS reported for both.

## 11.0 **RECORDS TO BE KEPT**

Records to be filed include the following:

1. Patient consent form
2. Registration form
3. Case report forms
4. Adverse event report form(s)
5. Follow-up assessments

The principal investigator will routinely review case report forms. Case report forms will be supported by primary source documents. All parties will maintain reports and all related documentation (or true copies of these documents) for a time period required by the applicable laws and regulations in the territories for which they are responsible, taking into account the minimum archiving period worldwide.

It is recommended to retain all documentation of adverse events, records of trial drug receipt and dispensation, and all IRB correspondence for at least 2 years after the investigation is completed.

## 12.0 **PATIENT CONSENT AND PEER JUDGMENT**

Current federal, NCI, state and institutional regulations regarding informed consent will be followed.

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**APPENDIX A: <sup>18</sup>F FDG PET evaluation form**

**Patient Name:** \_\_\_\_\_  
**Medical Record #** \_\_\_\_\_

Date of imaging study \_\_\_\_/\_\_\_\_/\_\_\_\_ Date of most recent chemotherapy \_\_\_\_/\_\_\_\_/\_\_\_\_

**Timing of PET scan:**

- ☐ After Cycle 4
- ☐ After Cycle 10
- ☐ Other \_\_\_\_\_

**Overall PET Result (for the presence of active tumor), based on 2007 IWG response criteria<sup>25</sup>:**

- ☐ Negative
- ☐ Positive

**Overall PET Result based on Deauville criteria<sup>27</sup>:**

- ☐ Negative
- ☐ Positive

**Deauville criteria** (for foci believed to represent tumor): evaluate maximum activity in tumor using mediastinal blood pool and normal liver as reference activity:

**Negative**

- ☐ 1 no abnormal activity (tumor cold compared with background)
- ☐ 2 minimal activity (tumor  $\leq$  mediastinal blood pool)
- ☐ 3 equivocal (tumor  $>$  mediastinal blood pool but  $\leq$  normal liver)

**Positive**

- ☐ 4 moderate activity (tumor moderately  $>$  normal liver)
- ☐ 5 strong activity (tumor markedly  $>$  normal liver or disease progression)

**Additional foci of activity**

Complete for scans other than baseline scan:

- ☐ Are there new foci of FDG activity? ☐ Yes ☐ No
- ☐ Are these judged to represent lymphoma? ☐ Yes ☐ No

**Comments:** \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

\_\_\_\_\_  
*Signature of radiologist*

\_\_\_\_/\_\_\_\_/\_\_\_\_  
*Date*

## **APPENDIX B: Radiation Treatment Guidelines**

The following are general guidelines for consolidative radiation therapy. The dose, schedule, and extent of radiation are at the discretion of the radiation oncologist.

### **Radiation Schedule**

#### Fractionation and start time

It is suggested that involved field radiation therapy consist of 30.6 Gy in 17 fractions of 1.8 Gy per day. Treatment is given daily, 5 days per week. Treatment should begin no later than 6 weeks after the last cycle, provided hematologic parameters are adequate.

#### Treatment breaks and blood counts

Treatment breaks are discouraged. However, radiation should be held if ANC < 500/uL or platelets < 25,000/uL and resumed upon adequate hematologic recovery.

### **Equipment**

#### Modality

Photon radiation should be used. In certain situations where a superficial lymph node is being treated, an electron beam may be used. IMRT is allowed on this study.

#### Energy

Megavoltage radiation should be used with accelerator beams with a nominal energy of at least 6 MV.

#### Geometry

The distance from the radiation source to the prescription point should be no less than 80 cm.

#### Calibration

All therapy units used in this protocol should have calibrations verified by the Radiological Physics Center.

### **Treatment Fields and Techniques**

The following target volumes are based on the International Commission on Radiation Units and Measurements (ICRU-50 and 62).

Gross Tumor Volume (GTV) is defined as all known areas of gross disease determined from CT and/or PET *after* chemotherapy (e.g., brentuximab vedotin). It will include any lymph node measuring > 1.5 cm in a single axis as defined on CT. If no disease is present following therapy (i.e., CR) then the GTV does not exist.

Clinical Target Volume (CTV) is defined as all areas of gross tumor (GTV) and involves initial lymph node volume *before* chemotherapy. It takes into account the initial location and extent of disease and will be defined based on the anatomic compartments defined below.

Planning Target Volume (PTV) is the CTV with an additional 0.5 to 1.0 cm margin to account for daily treatment set up, patient positioning, and internal organ motion. This expansion may be modified at the discretion of the treating radiation oncologist.

#### Beam Orientation

Treatment should be delivered through equally weighted AP/PA parallel opposed fields, though certain exceptions may exist and IMRT is allowed on this protocol.

### Treatment Position

Patients should be treated in the supine position with other positioning recommendations listed in the appropriate site-specific section below.

### Additional recommendations at simulation

IV contrast is strongly recommended for accurate identification of the vessels.

### Anatomic compartments:

#### Unilateral neck

The neck region includes both the cervical and supraclavicular lymph nodes. The involved side of the neck should be treated alone with the neck in the hyperextended position. The superior border should be 1-2 cm above the lower tip of the mastoid process and the inferior border should be 2 cm below the clavicle. The lateral border should include the medial 2/3 of the clavicle. The medial border is defined based on whether there is involvement of the supraclavicular nodes. If the supraclavicular nodes are not involved, the lateral border should be placed at the tip of the ipsilateral transverse process. If the supraclavicular nodes (or other medial nodes) are involved, then the lateral border should be placed at the contralateral transverse process.

#### Bilateral neck

Both sides of the neck are treated with the same head position, shielding, and superior and inferior borders as described in the unilateral neck section above.

#### Unilateral axilla

Arms should preferably be placed above the head to pull the axillary lymph nodes from the chest to allow for additional lung blocking. The superior border should be placed at the C5-C6 interspace or 2 cm above the pre-chemotherapy extent of disease. The inferior border should be placed at the tip of the scapula or 2 cm below the lowest axillary lymph node. The lateral border should flash the axilla. The medial border is defined based on involvement of supraclavicular lymph nodes. If there are no supraclavicular lymph nodes involved, then the medial border should be placed at the ipsilateral transverse process. If there is supraclavicular lymph node involvement, include the entire vertebral body.

#### Mediastinum +/- hila

The mediastinal region includes the mediastinum, bilateral hila, and bilateral supraclavicular lymph nodes. Arms should be placed akimbo or at the sides. Due to the risk of secondary breast cancer in female patients, the breast should be positioned laterally away from the field and taped for immobilization. The breast can also be outlined with a wire during simulation for better visualization and avoidance during treatment planning. The superior border should be placed at the C5-C6 interspace or the top of the larynx if the supraclavicular lymph nodes are involved. This border should be at least 2 cm above the pre-chemotherapy extent of disease. The inferior border should be 5 cm below the carina or 2 cm below the pre-chemotherapy extent of disease. The lateral border should be a 1.5 cm margin on the post-chemotherapy extent of disease. A 1 cm margin should be placed around the hilar region if not initially involved; otherwise, a 1.5 cm margin should be used.

#### Para-aortic lymph nodes

The superior border should be placed at the top of T11 and at least 2 cm above the pre-chemotherapy extent of disease. The inferior border should be placed at the bottom of L4 and at least 2 cm below the pre-chemotherapy extent of disease. The lateral borders should include the edge of the transverse processes and at least a 2 cm lateral to the post-chemotherapy volume. The spleen should only be treated if suggestive of disease involvement initially and is treated with a 1.5 cm margin around the post-chemotherapy volume. Both kidneys should be contoured on CT



simulation, identified for avoidance, and shielded as appropriate. When it is necessary to include one or both kidneys in the treated volume, keep the mean bilateral kidney dose to  $\leq 15$  Gy. Testicles should be shielded in men with a clamshell and consider oophoropexy for reproductive age women.

#### Pelvic lymph nodes

The pelvic region includes the external iliac, femoral, and inguinal lymph nodes. Patients should be simulated in a “frog-leg” position to separate the leg from the external genitalia and flatten any inguinal skin folds to minimize any potential skin reactions. The superior border should be at the middle of the sacroiliac joint or 2 cm above the pre-chemotherapy extent of disease. The inferior border should be below the pre-chemotherapy volume or 5 cm below the lesser trochanter. The medial border should be at least 2 cm medial to the pre-chemotherapy volume or may extend to include the medial border of the obturator foramen. The lateral border should be at least 2 cm lateral to the pre-chemotherapy volume or may extend to include the greater trochanter. If common iliac lymph nodes are involved, the superior border should be extended to the L4-L5 interspace with at least a 2 cm margin above the pre-chemotherapy lymph node volume. Testicles should be shielded in men with a clamshell and consider oophoropexy for reproductive age women.

#### **Dose calculations**

##### Dose definition

The suggested total dose to the prescription point is 30.6 Gy in 17 fractions of 1.8 Gy (180 cGy). Patients with residual disease following chemotherapy might receive an additional boost of 5.4 Gy in 3 fractions of 1.8 Gy for a total dose of 36 Gy.

##### Prescription points

For AP/PA parallel opposed beams, the prescription point is defined as a point along the central axis that is midway between the beam entrance and exit points.

**APPENDIX C: Adverse Event Reporting for Rituximab**

In addition to protocol Section 5.7, the following safety assessment and reporting guidelines apply to rituximab (RITUXAN), as specified by Genentech, Inc.:

**ASSESSMENT OF SAFETY****Specification of Safety Variables**

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to RITUXAN, all events of death, and any study specific issue of concern.

**Adverse Events**

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with Hodgkin lymphoma that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).

If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.

Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

**Serious Adverse Events**

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.)
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

**METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES**

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in

accordance with CFR 312.32 (IND Safety Reports).

### **Adverse Event Reporting Period**

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment and ends 6 months following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

### **Assessment of Adverse Events**

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the RITUXAN (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

#### **Yes**

There is a plausible temporal relationship between the onset of the AE and administration of RITUXAN, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to RITUXAN; and/or the AE abates or resolves upon discontinuation of RITUXAN or dose reduction and, if applicable, reappears upon re-challenge.

#### **No**

Evidence exists that the AE has an etiology other than the RITUXAN (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to RITUXAN administration (e.g., cancer diagnosed 2 days after first dose of RITUXAN).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert or current Investigator Brochure.

Unexpected adverse events are those not listed in the Package Insert (P.I.) or current Investigator Brochure (I.B.) or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

## **PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS**

### **Eliciting Adverse Events**

A consistent methodology for eliciting AEs at all subject evaluation timepoints should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

### **Specific Instructions for Recording Adverse Events**

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

**a. Diagnosis vs. Signs and Symptoms**

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is ok to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

**b. Deaths**

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death”.

**c. Preexisting Medical Conditions**

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

**d. Hospitalizations for Medical or Surgical Procedures**

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

**e. Post-Study Adverse Events**

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior RITUXAN exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

**f. Reconciliation**

The Sponsor agrees to conduct reconciliation for the product. Genentech and the Sponsor will agree to the reconciliation periodicity and format, but agree to exchange quarterly line listings of cases received by the other party. If discrepancies are identified, the Sponsor and Genentech will

cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution.

**g. SAE Reporting**

Investigators must report all SAEs to Genentech within the timelines described below. The completed Medwatch/case report should be faxed immediately upon completion to Genentech Drug Safety at:

**(650) 225-4682**  
**OR**  
**(650) 225-5288**

- Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.
- Serious AE reports that are related to RITUXAN will be transmitted to Genentech within fifteen (15) calendar days of the Awareness Date.
- Serious AE reports that are unrelated to RITUXAN will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.
- Additional Reporting Requirements to Genentech include the following:
- Any reports of pregnancy following the start of administration with RITUXAN will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.

**h. Non-Serious AE Reporting**

All non-serious Adverse Events originating from the Study will be forwarded, in a quarterly report to Genentech.

***Note: Investigators should also report events to their IRB as required.***

**MedWatch 3500A Reporting Guidelines**

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

**Follow-up Information**

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom and adverse event was reported. For questions regarding SAE

reporting, you may contact the Genentech Drug Safety representative noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at <http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm>

### **Additional Reporting Requirements for IND Holders**

For Investigator-Sponsored IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

#### **7 Calendar Day Telephone or Fax Report**

The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of RITUXAN. An unexpected adverse event is one that is not already described in the RITUXAN Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

#### **15 Calendar Day Written Report**

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of RITUXAN. An unexpected adverse event is one that is not already described in the RITUXAN investigator brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a Medwatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

#### **FDA fax number for IND Safety Reports:**

Fax: 1 (800) FDA 0178

#### **All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to Genentech Drug Safety:**

Fax: (650) 225-4682 or (650) 225-5288

#### **And to the Site IRB:**

Fax: (410) 955-4367 or (443) 287-5353

**For questions related to safety reporting, please contact Genentech Drug Safety:**

Tel: (888) 835-2555

Fax: (650) 225-4682 or (650) 225-5288

**IND Annual Reports****Copies to Genentech:**

All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. Copies of such reports should be faxed to Genentech Drug Safety:

Fax: (650) 225-4682 or (650) 225-5288

**STUDY CLOSE-OUT**

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

**Rituxan Clinical Operations Group****Fax: 650-745-7373****Email: [rituxan-qsur@gene.com](mailto:rituxan-qsur@gene.com)****SAFETY REPORTING REQUIREMENTS FOR IND EXEMPT STUDIES**

For **Investigator Sponsored IND Exempt Studies**, there are some reporting requirements for the FDA in accordance with the guidance set forth in 21 CFR 314.80.

*Postmarketing 15-Day "Alert Report":*

The Sponsor-Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is **unexpected and assessed by the investigator to be possibly related to the use of Rituximab**. An unexpected adverse event is one that is not already described in the Investigator Brochure. Such reports are to be submitted to the FDA (2 copies) at the following address: Central Document Room, 12229 Wilkins Avenue, Rockville, MD 20852.

All Postmarketing 15-Day "Alert Reports" submitted to the FDA by the Sponsor-Investigator must also be faxed to:

Genentech Drug Safety

Fax: (650) 225-4682 or (650) 225-4683

(Please use the safety reporting fax cover sheet attached to this document for your fax transmission. Also provided on Rituxan CD-ROM)

**For questions related to safety reporting, contact:**

Genentech Drug Safety

Tel: 1-888-835-2555

Or

Fax: (650) 225-4682 or (650) 225-4683

(Please use the safety reporting fax cover sheet attached to this document for your fax transmission)

**APPENDIX D:****SAFETY REPORTING FAX COVER SHEET****Genentech Supported Research****AE / SAE FAX No: (650) 225-4682****Alternate Fax No: (650) 225-5288**

<b>Genentech Study Number</b>	
<b>Principal Investigator</b>	
<b>Site Name</b>	
<b>Reporter name</b>	
<b>Reporter Telephone #</b>	
<b>Reporter Fax #</b>	

<b>Initial Report Date</b> (DD/MON/YYYY)	____ / ____ / ____
<b>Follow-up Report Date</b> (DD/MON/YYYY)	____ / ____ / ____

<b>Subject Initials</b> (Please enter a dash if patient has no middle name)	____ / ____ / ____
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SAE or Safety Reporting questions, contact Genentech Safety: (888) 835-2555

***PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET****Page 1 of \_\_\_\_*